[I/V]HCXAGXXR[S/T]G SEQ ID NO: 1,

that is invariant among all PTPs. The cysteine residue in this motif is invariant in members of the family and is known to be essential for catalysis of the phosphotyrosine dephosphorylation reaction. It functions as a nucleophile to attack the phosphate moiety present on a phosphotyrosine residue of the incoming substrate. If the cysteine residue is altered by site-directed mutagenesis to serine (*e.g.*, in cysteine-to-serine or "CS" mutants) or alanine (*e.g.*, cysteine-to-alanine or "CA" mutants), the resulting PTP is catalytically deficient but retains the ability to complex with, or bind, its substrate, at least *in vitro*.

Please replace the paragraph beginning at page 11, line 16 and ending at line 25, with the following rewritten paragraph:

Figure 1 shows a multiple amino acid sequence alignment of the catalytic domains of various PTPs. The positions of amino acid residues of PTP1B that interact with substrate are indicated with small arrowheads, and the residue numbering at the bottom of the alignment corresponds to that for PTP1B. Figs. 1A-1E show a multiple sequence alignment of the catalytic domains of PTPs (SEQ ID NOS:2-36). Cytosolic eukaryotic PTPs and domain 1 of RPTPs are combined into one group; domains 2 of RPTPs are in a second group and the *Yersinia* PTP is in a third. Invariant residues shared among all three groups are shown in lower case. Invariant and highly conserved residues within a group are shown in italics and bold, respectively. Within the *Yersinia* PTP sequence, residues that are either invariant or highly conserved between the cytosolic and RPTP domain sequences are in italics and bold, respectively.

Please replace the paragraph beginning at page 15, line 13 and ending at line 19, with the following rewritten paragraph:

(Twice Amended) As defined herein, a phosphatase is a member of the PTP family if it contains the signature motif [I/V]HCXAGXXR[S/T]G (SEQ ID NO: 1). Dual specificity PTPs, *i.e.*, PTPs which dephosphorylate both phosphorylated tyrosine and

phosphorylated serine or threonine, are also suitable for use in the invention. Appropriate PTPs for use in the present invention may be any PTP family member including, but not limited to, PTP1B, PTP-PEST, PTPγ, MKP-1, DEP-1, PTPμ, PTPX1, PTPX10, SHP2, PTP-PEZ, PTP-MEG1, LC-PTP, TC-PTP, CD45, LAR and PTPH1, and mutated forms thereof.

Please replace the paragraph beginning at page 16, line 4 and ending at page 16, line 24, with the following rewritten paragraph:

(Twice Amended) As noted above, substrate trapping mutant PTPs are derived from wildtype PTPs that have been mutated such that the wildtype protein tyrosine phosphatase catalytic domain invariant aspartate residue is replaced with an amino acid which does not cause significant alteration of the Km of the enzyme but which results in a reduction in Kcat to less than 1 per minute. Optionally, a catalytic domain cysteine residue is also replaced with a different amino acid, and/or at least one wildtype tyrosine residue is replaced with an amino acid that is not capable of being phosphorylated. In this regard, amino acid sequence analysis of known PTPs reveals the presence of twenty-seven invariant residues within the PTP primary structure (Barford *et al.*, 1994 *Science 263*:1397-1404; Jia *et al.*, 1995 *Science 268*:1754-1758), including an aspartate residue in the catalytic domain that is invariant among PTP family members. When the amino acid sequences of multiple PTP family members are aligned (see, for instance, Figure 1A-E in U.S.A.N. 09/334,575; see also, *e.g.*, Barford *et al.*, 1995 *Nature Struct. Biol.* 2:1043), this invariant aspartate residue may be readily identified in the catalytic domain region of each PTP sequence at a corresponding position relative to the PTP signature sequence motif [I/V]HCXAGXXR[S/T]G (SEQ ID NO:1), which is invariant among all PTPs (see, *e.g.*, WO98/04712; Flint *et al.*, 1997 *Proc. Nat. Acad. Sci.* 94:1680 and references cited therein). However, the exact amino acid sequence position numbers of catalytic domain invariant aspartate residues may be different from one PTP to another, due to sequence shifts that may be imposed to maximize alignment of the various PTP sequences (see, *e.g.*, Barford *et al.*, 1995 *Nature Struct. Biol. 2*:1043 for an alignment of various PTP sequences).

In the Claims:

Please cancel claims 2, 6 and 7.

Please amend claims 1 and 8 to read as follows:

1. (Amended) A method for identifying an agent which alters the interaction between a protein tyrosine phosphatase and a tyrosine phosphorylated polypeptide which is a substrate of the protein tyrosine phosphatase, comprising:

(a) contacting in the absence and in the presence of a candidate agent, a substrate trapping mutant of a protein tyrosine phosphatase and a detectably labeled tyrosine phosphorylated peptide which is a substrate of the protein tyrosine phosphatase under conditions and for a time sufficient to permit formation of a complex between the tyrosine phosphorylated peptide and the substrate trapping mutant protein tyrosine phosphatase, wherein the substrate is capable of generating a fluorescence energy signal and wherein the substrate trapping mutant protein tyrosine phosphatase is selected from the group consisting of

(i) a protein tyrosine phosphatase in which wildtype protein tyrosine phosphatase catalytic domain invariant aspartate residue is replaced with an amino acid which does not cause significant alteration of the Km of the enzyme but which results in a reduction in Kcat to less than 1 per minute, and

(ii) a protein tyrosine phosphatase in which a cysteine that is present in a signature sequence motif as set forth in SEQ ID NO:1 within a wildtype protein tyrosine phosphatase catalytic domain is mutated at an amino acid position occupied by a cysteine residue; and

(b) comparing the fluorescence energy signal level in the absence of the agent to the fluorescence energy signal level in the presence of the agent, wherein a difference in the fluorescence energy signal level indicates the agent alters formation of a complex between the protein tyrosine phosphatase and the substrate, and wherein the fluorescence energy signal is a fluorescence polarization signal.

8. (Amended) The method of claim 1 wherein the substrate trapping mutant protein tyrosine phosphatase comprises a protein tyrosine phosphatase in which at least